

**Management of severe oligohydramnios with antepartum transabdominal
amnioinfusion**

Norbert Pásztor MD

PhD Thesis

Szeged

2014

**University of Szeged,
Department of Obstetrics and Gynecology**

Tutors:

Professor Attila Pál MD, PhD

Gábor Németh MD, PhD

List of publications related to the Thesis

I.

Kozinszky Z, **Pásztor N**, Vanya M, Sikovanyecz J, Pál A. Management of severe idiopathic oligohydramnios: is antepartum transabdominal amnioinfusion really a treatment option? J Matern Fetal Neonatal Med. 2013;26(4):383-7. **IF: 1.518**

II.

Pásztor N, Keresztúri A, Kozinszky Z, Pál A. Identification of causes of stillbirth through autopsy and placental examination reports. Fetal Pediatr Pathol. 2014;33(1):49-54. **IF: 0.580**

III.

Kozinszky Z, Sikovanyecz J, **Pásztor N**. Severe midtrimester oligohydramnios: treatment strategies. Curr Opin Obstet Gynecol. 2014;26(2):67-76. **IF: 2.637**

IV.

Pásztor Norbert dr, Sikovanyecz János dr, Kozinszky Zoltán dr, Németh Gábor dr, Pál Attila dr. Az antepartum transzabdominális amnioinfúzió szerepe a súlyos oligohydramnion kezelésében (The role of antepartum transabdominal amnioinfusion in the management of severe oligohydramnios) [in Hungarian] Magy Nőorv L (accepted for publication)

Cumulative Impact Factor of listed publications: 4.735

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Abbreviations

AF:	amniotic fluid
AFI:	amniotic fluid index
AFV:	amniotic fluid volume
AP:	amniopatch
APTA:	antepartum transabdominal amnioinfusion
BMI:	body mass index
CI:	confidence interval
CS:	cesarean section
GA:	gestational age
IUGR:	intrauterine growth retardation
IVF-ET:	<i>in vitro</i> fertilization and embryo transfer
LGA:	large for gestational age
NEC:	necrotizing enterocolitis
n.s.:	statistically not significant
OR:	odds ratio
PPROM:	preterm premature rupture of the membranes
iPPROM:	iatrogenic preterm premature rupture of the membranes
sPPROM:	spontaneous preterm premature rupture of the membranes
RDS:	respiratory distress syndrome
S.D.:	standard deviation
SDP:	single deepest pocket
TAAC:	transabdominal amniocentesis
TA-CVS:	transabdominal chorion villous sampling

Introduction

Role of the amniotic fluid

The amniotic fluid (AF) provides an ideal environment for fetal development and growth. It protects the fetus from trauma, and allows normal movements, which is important for musculoskeletal development. The AF provides the fetus with a source of water, participates in the fetal metabolism, maintains a constant temperature and plays a crucial role in the development of the fetal lungs^{1,2}.

The AF is predominantly composed of water³. It is of prime importance that the AF composition appears to be under much tighter control than that of the AF volume (AFV). Abnormalities of composition are much rarer than those of volume, and in most cases of abnormality of volume the composition is normal for the gestational age (GA)⁴. During the first trimester, the composition of the AF is very similar to that of the extracellular fluid of the fetus; it is isotonic with the maternal or fetal plasma, but contains minimal protein⁵. It demonstrates an extremely low oxygen tension and high concentrations of sugar alcohols, because of the anaerobic metabolism⁶. With advancing gestation, its composition diverges from that of the plasma. Its osmolality and sodium concentration decrease, an effect thought to be a result of the production of dilute fetal urine. It has been well demonstrated that the fetal urine becomes increasingly hypotonic relative to the fetal plasma as gestation progresses, due to the relatively large glomerular filtration for the renal blood flow in the fetal metanephros⁷. Parallel to the decrease in osmolality, the urea, creatinine and uric acid contents of the AF increase during the second half of pregnancy⁸.

Together with the changes in content, the AFV changes dramatically during pregnancy. The average AFV increases progressively from 1.5 ml at 7 weeks to 20-25 ml at 10 weeks⁹⁻¹¹, 630 ml at 22 weeks and 770 ml at 28 weeks of gestation¹⁰. At the beginning of pregnancy, the AFV is a multiple of the fetal volume, but they become equal after 20 weeks³. Between 29 and 37 weeks, there is only a slight change, with a peak around 34 weeks, and the AF subsequently decreases during the pregnancy^{10,12}. At 30 weeks the AFV is about half and at term it is about a quarter of the fetal volume³.

During the early weeks of pregnancy, the AF is a result of secretion from the amniotic or chorionic epithelium and the transfer of water across the fetal skin and umbilical vessels¹¹. Fetal urine enters the amniotic space around week 8, and from the weeks 10-12 the fetal kidneys assume an increasing role in the regulatory process³. The AFV is the resultant of the inflow and the outflow in the amniotic space. The total AFV is exchanged within 3 h². As compared with the early stages of pregnancy, much more is known about the pathways involved in this regulation during the second half of gestation, after keratinization of the fetal skin.

Production of the amniotic fluid during the second half of gestation

1. Urine production

It is obvious that the fetal urine is the predominant source of the AF, as evidenced by the almost complete absence of AF in the event of renal agenesis¹³. The amount of urine produced can be estimated through the ultrasonographic assessment of the fetal bladder volume¹⁴⁻¹⁸. The latest studies indicate that in normal pregnancies the fetal urine production at 25 weeks is approximately 7.5 ml/h, and at 40 weeks it is 71.4-125.1 ml/h¹⁶⁻¹⁸. A correlation has been found between the fetal urinary product and the fetal weight¹⁹, and the urine production can therefore be predicted via the simple measurement of biometric parameters¹⁹. It has been demonstrated that the fetal urine contains an active substance which stimulates the intramembranous transport of the AF across the amnion into the underlying fetal vasculature²⁰, and thus the fetal urine takes part not only in the production, but also in the elimination of the AF. The urine production can be affected by several factors. In complicated pregnancies, the urine production can change appreciably²¹⁻²³, which strongly affects the AFV.

2. Fetal lung fluid production

The rate of fluid production by the human fetal lungs has not been measured, and the available data are derived from the ovine fetus. During the last third of gestation, the fetal lamb secretes an average fluid volume of 100 ml/day/kg from the lungs. Half of this liquid mixes with the AF and half is swallowed. Around 18% of the swallowed fluid is derived from the fetal lungs²⁴. Under physiological conditions, the total lung fluid production is about one-third of the urine production and the AF contribution is only one-sixth of the urine¹. The secretion rate has been shown to be influenced predominantly by hormones and neural

transmitters such as catecholamines²⁵, arginine-vasopressin²⁶ and cortisol²⁷. It has been reported that the secretion rate is unaltered in the case of a rapidly reduced AFV²⁸, but a chronic AFV decrease results in a reduced lung fluid secretion rate²⁹. The fluid production seems to be fairly constant at a maximum rate, and the modulation of lung fluid production is therefore unlikely to be a significant modulator of the AFV. It is most important in serving for pulmonary expansion, which is necessary in normal airway and alveolar development¹.

3. Transmembranous pathway of fluid exchange

On the basis of compartmental analysis, it was assumed that there is an exchange of water between mother and conceptus by ways outside the fetal-placental circulation³⁰. This exchange involves diffusion and the filtration of water³¹ and it occurs across the fetal membranes between the AF and the maternal blood within the wall of the uterus³². The expression „transmembranous pathway” is used to describe this phenomenon. The contribution of this pathway changes with advancing gestation since the net volume transfer across the membranes is inward early in gestation and outward during late gestation. As compared with other factors in the AF regulation (e.g. fetal urine, lung secretion and fetal swallowing), there is little support for a significant contribution of transmembranous fluxes to the AFV and composition in the second half of gestation³².

Elimination of the amniotic fluid during the second half of gestation

The elimination of the AF involves two main regulatory mechanisms.

1. Fetal swallowing

Fetal swallowing has been demonstrated to be a secondary contributor in AFV regulation. The human fetus swallows an average of 210-760 ml/day³³ and, within certain limits, this mechanism can afford protection from the development of either oligohydramnios or polyhydramnios³⁴. Although fetal sheep with a ligated esophagus can maintain the normal AFV under experimental circumstances³⁵, in cases of esophageal or intestinal atresia polyhydramnios usually develops in human pregnancies³⁶.

2. Intramembranous pathway of fluid exchange

In the second half of pregnancy, „intramembranous” fluid exchange is important; this is large in magnitude and plays a major role in regulating both the AFV and the composition^{37,38}. The regulatory function of this pathway even outweighs the role of fetal

swallowing. Intramembranous absorption allows the movement of the AF and solutes directly to the fetal blood. This occurs through a microscopic network of fetal blood vessels on the fetal surface of the placenta^{39,40}. Based on a mathematical model, the basal intramembranous absorption in the late-gestation ovine fetus is 200-400 ml/day³², and a similar extent can be assumed in the human fetus⁴¹. Under experimental conditions, in the event of AFV loading, the intramembranous absorption increases dramatically as a compensatory mechanism^{32,42}. Some of this absorption occurs passively, because the AF is hypo-osmotic with respect to the fetal plasma, but an active component of this fluid exchange has also been demonstrated⁴²⁻⁴⁴. Water can enter the fetal circulation from the AF through either paracellular or transcellular routes. In the regulation of the paracellular flux, changes in the amniotic tight junctions may have a central role⁴⁵, while the transcellular routes are controlled by aquaporin transmembrane channels^{44,46}.

Assessment of the amniotic fluid volume in clinical practice

Oligohydramnios is believed to complicate 4-4.9% of pregnancies⁴⁷. Oligohydramnios has six possible major causes: 1) a severe fetal abnormality, 2) preterm premature rupture of the membranes (PPROM), 3) an isolated/idiopathic form, 4) an impaired placental function leading to insufficiency, 5) a complication of multiple pregnancies, and 6) iatrogenic⁴⁸. There are two peaks in the incidence of oligohydramnios, between weeks 13 and 21 and between weeks 34 and 42⁴⁹. The AFV can be measured by dye dilution techniques at the time of amniocentesis⁵⁰, or can be measured directly measured at cesarean section (CS)⁵¹. Dye-determined AF measurements may give sufficiently accurate results, but there have been only a very limited number of investigations to date. This method is not appropriate for daily clinical routine, and the AFV is therefore estimated by ultrasonography. The AF index (AFI) varies with the GA⁵², and oligohydramnios is defined as a deficiency of AFV below the 5th percentile corresponding to the GA^{53,54}. Besides the subjective estimation, two methods of assessment are frequently used in clinical practice: 1) the AFI⁵², and 2) measurement of the single deepest pocket (SDP)⁵⁵.

1. Amniotic fluid index

During the measurement with this method, the amniotic cavity is virtually divided into four quadrants and the sum of the vertical diameters of these four areas gives the AFI. Several studies have indicated an increased risk of adverse pregnancy outcome when the AFI is 5 cm or less⁵⁶⁻⁵⁹.

2. Single deepest pocket

In the SDP method, the largest AF pocket is measured vertically. Chamberlain et al. evaluated the relationship of a SDP as an antenatal test in high-risk pregnancies, and found that the perinatal mortality increases with the severity of oligohydramnios⁵⁵. During antepartum fetal surveillance, use of the SDP method resulted in a significantly lower rate of suspected as oligohydramnios compared with the AFI⁶⁰⁻⁶². Both methods are currently frequently used in clinical practice.

My investigation focused on the importance of oligohydramnios and the possibilities of its management. This thesis consists of three main parts:

1. Assessment of oligohydramnios, other maternal and fetal risk factors and causes of death in pregnancies complicated with intrauterine fetal death.
2. Meta-analysis of relevant publications on the treatment of oligohydramnios between 13-26 weeks of pregnancy. Expectant management, transabdominal amnioinfusion and amniopatch technique were compared especially in terms of survival, pulmonary hypoplasia and postural deformities.
3. Observational study on the outcome of transabdominal amnioinfusion in case of idiopathic oligohydramnios between 16-34 weeks in our pregnant population.

Analysis of oligohydramnios and other risk factors in cases with stillbirth through autopsy and placental examination reports

Introduction

In the third trimester, oligohydramnios has been reported to associated with increased level of labor induction, stillbirth, a nonreassuring fetal heart rate, iatrogenic premature delivery, meconium aspiration syndrome, admission to a neonatal intensive care unit and neonatal death^{55,57-59,63-65}. On the other hand, the association between oligohydramnios and neonatal acidosis has not been sufficiently demonstrated; the observed adverse perinatal outcome results can be explained by the unnecessarily aggressive obstetrical management in the case of a reduced AF^{59,62}. Other authors have found oligohydramnios to be a significant risk factor for an adverse perinatal outcome only in the presence of intrauterine growth

retardation (IUGR)^{66,67}, while isolated oligohydramnios in the third trimester does not seem to involve a risk of perinatal morbidity^{68,69}.

Aims

There is no unequivocal conclusion regarding the effect of oligohydramnios on the pregnancy outcome in the third trimester. For our analysis, we chose the population of pregnancies complicated with intrauterine fetal death. Our aims were: 1) to identify the causes of stillbirth; 2) to analyze the association between this adverse outcome and pathologic obstetrical conditions such as oligohydramnios; and 3) to specify risk factors for intrauterine fetal death.

Materials and methods

We carried out a retrospective analysis on the total number of stillbirths that occurred at the Department of Obstetrics and Gynecology, University of Szeged, Hungary, between 1996 and 2010. Only cases with a GA of 24 weeks or more were surveyed, and also stillbirths with a birth weight of at least 500 g if the GA was unknown. The GA was determined from the last menstrual period and confirmed or adjusted by ultrasonographic measurement of the fetal crown-rump length (8-10 weeks) or the biparietal diameter (12-20 weeks). The pregnancy characteristics and the comprehensive autopsy results were collected from the medical charts. The medical charts furnished the date of the delivery, the GA, the birth weight and the pregnancy details.

The autopsies and placental histopathological examinations performed by the pathologists clearly demonstrated the cause of fetal death in most of the cases, but the clinical course was also considered. Subsequently, the cause of stillbirth was determined by a consensus between the gynecologists on the basis of relevant clinical findings that can explain subsequent stillbirth and the pathologists who reported the autopsy and placental histopathological results.

IUGR was defined as a fetal weight below the 10th percentile, and a large for gestational age (LGA) fetus was defined as a fetal weight above the 90th percentile, using the Hungarian fetal growth and birth weight centiles².

Placental insufficiency was characterized by inadequate spiral artery remodeling and/or spiral artery pathology leading to a uteroplacental vascular insufficiency, such as (1) an

acute placental infarction ($> 20\%$) and/or (2) calcification ($> 20\%$), or (3) a placental hematoma with intervillous thrombosis. The placental insufficiency group included morphological abnormalities that arose because of abnormal developmental processes and acquired placenta parenchyma disorders that affected $> 20\%$ of the villi/intervillous space (as classified at the Department of Pathology, University of Szeged). Placental lesions were also recorded by the pathologists when these histopathological observations did not reach a level of 20% and were not so severe as to cause stillbirth. An infectious cause of death was defined as autopsy evidence of organ involvement with an infectious organism and/or a histological placental examination with infectious findings⁷⁰.

The relationships between the fetal and the maternal characteristics were analyzed by means of the χ^2 test. Statistical significance was defined at the two-sided $p = 0.05$ level.

Results

Overall 140 stillbirths and 29,897 births occurred during the 15-year period, representing an average stillbirth rate of 4.7 per 1000. One hundred and twenty-six of the 140 stillbirths (90.0%) occurred in singular pregnancies, and the remaining 14 (10.0%) in twin pregnancies. The median GA at delivery was 31 weeks (range: 24-40 weeks), whereas two postdate stillbirths were recorded. The median maternal age was 28 years (range: 18-45 years). Hypertensive disorders were present during pregnancy in 27 cases (19.3%), while diabetes occurred during pregnancy in 13 cases (9.2%). The incidences of the maternal risk factors are listed in Table 1. The most common fetal finding was IUGR, which was demonstrated in 67 of the 140 cases (47.8%). Oligohydramnios was diagnosed in 14 cases (10.0%) and the fetus was LGA in 12 cases (8.6%). A lethal abnormality was noted in 3.6% (5/140) of the cases. The incidences of the fetal risk factors are illustrated in Table 2.

Both autopsy and placental histological results were available on 137 of the 140 cases (97.9%). The postmortem examination revealed the cause of death in 81 cases (57.9%), while 56 cases (40.0%) remained unexplained (mean GA \pm standard deviation (S.D.): 31.03 ± 4.29 weeks). The results of the autopsy and the histological examinations of the placenta are presented in Table 3.

As regards the explained cases (mean GA \pm S.D.: 30.21 ± 3.50 weeks), the cause of death was placental insufficiency in 38 of the 81 cases (46.9%, mean GA \pm S.D.: 30.21 ± 3.50 weeks), an umbilical cord complication (an umbilical cord knot, or a constricting loop around the

neck) in 21 cases (25.9%, mean GA \pm S.D.: 32.81 ± 5.0 weeks), an infection in 8 cases (9.9%, mean GA \pm S.D.: 29.37 ± 4.57 weeks), lethal congenital malformations in 5 cases (6.2%, mean GA \pm S.D.: 32.4 ± 5.08 weeks), placental abruption in 5 cases (6.2%, mean GA \pm S.D.: 32.6 ± 4.45 weeks) and hydrops fetalis in 4 cases (4.9%, mean GA \pm S.D.: 29.0 ± 3.56 weeks).

Table 1. Incidence of maternal risk factors

Maternal age (year) (mean \pm S.D.)	28.5 \pm 6.0	
Gestational age at stillbirth (week)	31.2 \pm 4.0	
Maternal risk factor	N = 140	
	n	%
Maternal obesity ^a	31	22.1
Inadequate antenatal care ^b	29	20.7
Hypertensive disorder ^c	27	19.3
Advanced maternal age (>35 years)	22	15.7
Maternal smoking	21	15.0
Gestational diabetes mellitus	10	7.1
Recurrent early pregnancy loss	7	5.0
Pregnancy after IVF-ET	6	4.3
Previous stillbirth	5	3.6
Type1 diabetes mellitus	3	2.1

^a: Maternal obesity is defined as a body mass index (BMI) > 30 kg/m²; ^b: Number of antenatal care visits \leq ; ^c: Including all grades of pre-eclampsia, pregnancy-induced hypertension and essential hypertension; S.D.: standard deviation; IVF-ET: in vitro fertilization and embryo transfer

Table 2. Incidence of fetal risk factors

Fetal risk factor	N = 140	
	n	%
IUGR fetus	67	47.8
Oligohydramnios	14	10.0
LGA fetus	12	8.6
Lethal congenital anomaly	5	3.6
Isoimmunization	2	1.9
Placenta previa	2	1.9
Hydramnios	1	0.9

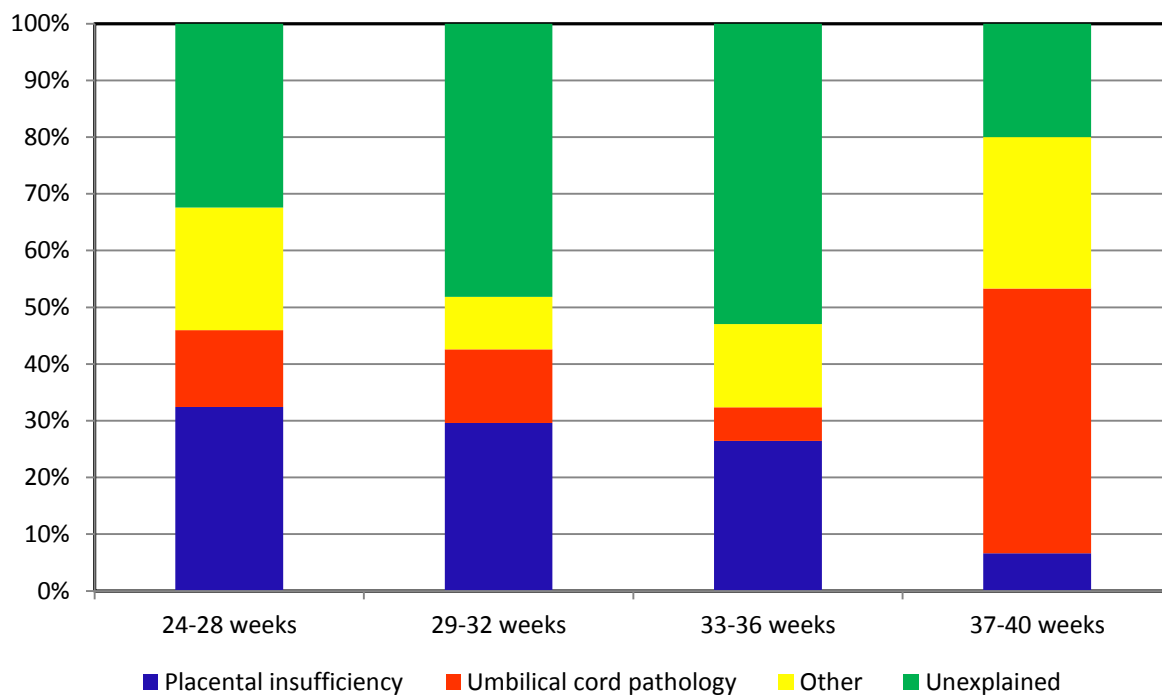
IUGR: intrauterine growth retardation; LGA: large for gestational age

Table 3. Causes of fetal death (autopsy and/or placental histological results)

Cause of death	N = 140	
	n	%
Placental insufficiency	38	27.1
Umbilical cord origin	21	15.0
Fetal infection	8	5.7
Lethal congenital anomaly	5	3.6
Placental abruption	5	3.6
Hydrops fetalis	4	2.9
Unexplained	56	40.0
Either autopsy or histological examination of the placenta not performed	3	2.1

Placental lesions were recorded in 78 cases, but only 48.7% reached a level that could have led to stillbirth, whereas almost half of the unidentified cases (44.1%) exhibited pathological placental lesions. The categories of the causes of death by GA are illustrated in Figure 1. Unexplained deaths occurred predominantly up to 36 weeks of gestation.

The prevalence of a placental insufficiency displayed a decreasing tendency throughout pregnancy. The proportion of stillbirths classified as involving umbilical cord pathology was highest in late pregnancy.

Figure 1. Categories of causes of death by gestational age

A fetal infection was typically present at a lower GA, whereas lethal congenital abnormalities and placental abruption tended to complicate the pregnancies at a later stage.

Discussion

To date, this is the first study published on the causes and risk factors of fetal death in Eastern-Central Europe. Fetal death is a sensitive obstetric care indicator and stillbirth still plays a major role in perinatal mortality⁷¹. The stillbirth rate worldwide varies from 2.1 per 1000 to 40 per 1000 births^{71,72}, and our rate of 4.7 per 1000 is in concordance with the data obtained from other high-income regions of the world⁷².

Despite our high autopsy/placental examination rate (97.9%), the number of unexplained stillbirths was still 42.1% of the total. In other studies, the rate of stillbirths with no apparent cause varied between 23.2 and 66.2%^{70,73,74}, but the rate of unexplained stillbirths and the distribution of cases into causes of death groups varies depending on the classification system used⁷⁵.

The most frequent maternal risk factors were maternal obesity, lack of adequate antenatal care and hypertensive disorders. From previous studies, it is clear that a relationship exists between maternal obesity and adverse pregnancy outcomes⁷⁶⁻⁷⁸. Maternal overweight (BMI = 25-30 kg/m²) and obesity (BMI > 30 kg/m²) pose an increased risk of fetal death^{76,78}. Adult obesity rates in Hungary are amongst the highest in the OECD (Organization for Economic Co-operation and Development) area: about 27.6% of Hungarian women are obese⁷⁹. Lack of antenatal care is an important risk factor of an adverse pregnancy outcome such as preterm birth, low birth weight and perinatal death⁸⁰⁻⁸². In our dataset, every fifth women (20.7%) had no adequate prenatal care during her pregnancy. An earlier study from our department revealed that the occurrence of uncared pregnancies in the population was 1.0%⁸⁰. Comparing these results, the contribution of the antenatal care system in stillbirth prevention is more emphasized. Several studies have confirmed that there is an increased risk of stillbirth in the event of hypertensive disorder in pregnancy⁸³⁻⁸⁶, independently of the type of hypertension. A meta-analysis of studies on pre-existing hypertension demonstrated a rise in the odds of stillbirth of around 2.6 times^{76,85}. Pregnancy-induced hypertension was associated with a 30% increase, while pre-eclampsia was associated with a 60% rise in the odds for stillbirth compared to normotensive pregnancies^{76,83,84,86}. These results are consistent with our data. In our stillbirth dataset, the occurrence of all types of hypertensive disorders

was 19.3%, and the majority were pregnancy-induced hypertension or pre-eclampsia, since they occurred in 15.7% of the cases.

Growth disorders are the most important fetal risk factors in stillbirth. In our study, almost half of the cases (47.8%) involved IUGR, while 8.6% were LGA. IUGR is associated with a 4-times higher risk of stillbirth⁷⁶, and its proportion in our study is in concordance with other results which report the occurrence of 37.5-46.8% growth restriction in stillbirth⁸⁷⁻⁹⁰. Although it is possible to screen pregnancies for IUGR with ultrasonography, current antenatal detection rates of IUGR are reported to be only 25-36%⁹¹⁻⁹³. Thus, more effective screening of fetal growth disorders could well play a pivotal role in the prevention of fetal deaths. In our study, however, in pregnancies with IUGR, the average GA was 30.6 ± 3.4 weeks, and one-third of the stillbirth cases involving IUGR occurred before 28 weeks. It should be noted that it is highly debatable that stillbirth may be prevented through labor induction or even operative delivery in this critically early period of the third trimester.

In our sample, the most frequent cause of stillbirth was a placental insufficiency, which occurred in 46.9% of the explained cases, in accordance with the 49.9% reported by Korteweg et al.⁷⁵. The high frequency of pathological conditions of the placenta in fetal death cases may suggest causality between the placental pathology and fetal demise^{74,75,87}. Placental disease could be the primary cause of abnormal fetal development and poor fetal growth. These histopathological findings could be present in a placenta in an uncomplicated pregnancy, but their grades are enhanced in pregnancies complicated with stillbirth⁹⁴.

Oligohydramnios occurred in 10% of the cases and appeared to be a noteworthy factor in fetal death. This prevalence is at least double that reported in population studies^{47,95}. It is of paramount importance that oligohydramnios was significantly associated with IUGR: 78.6% of the fetuses with oligohydramnios were growth-retarded. No other condition was found to be associated with a low AFV. In the group of stillbirths, we found a significant difference between the fetal weight with oligohydramnios and without (871 ± 648 g vs. 1619 ± 910 g; $p = 0.006$), but there was not a significant difference regarding the placental weight with and without low AFV (248 ± 126 g vs. 336 ± 161 g; $p = 0.24$). Our result seems to support the observation of Apel-Sarid et al.⁶⁶, who found oligohydramnios to be a significant risk factor for an adverse perinatal outcome in pregnancies complicated with IUGR. Nevertheless, they were not able to present any differences in placental pathologies by comparing cases with or without oligohydramnios. The role of a reduced AFV in the prediction of fetal death is still

questionable. The fundamental work of Chamberlain et al. demonstrated a more than 55-fold increase in perinatal mortality if serious oligohydramnios was present⁵⁵. Several studies found oligohydramnios to be an independent risk factor of intrauterine fetal death^{56,65,96}. Chhabra et al.⁹⁷ reported a perinatal mortality of 18% in a group of high-risk pregnancies with oligohydramnios. However, the suggestion has emerged that the observed adverse perinatal results may be explained by the unnecessarily aggressive obstetrical management^{59,62,63,98}. The confusing data on the predictive value of oligohydramnios for adverse outcomes can be explained by the difference in pregnancies with a reduced AFV. Zhang et al.⁶⁹ demonstrated that oligohydramnios with unfavorable maternal and/or fetal conditions, such as IUGR, fetal anomalies or hypertensive disorders, leads to a much worse perinatal outcome than a normal AFV with the same conditions (perinatal mortality 5.1% vs. 1.2%). However, they found that about half of the oligohydramnios cases did not have any coexisting medical or obstetric conditions. Fetuses in these cases tend to be appropriately sized at the diagnosis of isolated oligohydramnios and their perinatal outcomes are similar to those of pregnancies with a normal AFV⁶⁹. The occurrence of such isolated oligohydramnios is more frequent at term^{49,68,99}, which can be an additive factor toward a better outcome.

Treatment strategies for severe second and early third trimester oligohydramnios

Introduction

Several stages of fetal lung development can be distinguished on the basis of the histological lung morphology: the embryonal, pseudoglandular, canalicular, saccular and alveolar phases. As the transitions between these stages are fluent, the schedule of lung growth is quite arbitrary. The tree of conducting airways has fully developed by a GA of 16 weeks¹⁰⁰. The subsequent canalicular phase is characterized by a widening of the airway lumina, the growth of respiratory airways, and a flattening of the gas-exchanging epithelium, which is accompanied by a growth spurt of the distal pulmonary vasculature. Massive angiogenesis leads to a dense capillary network surrounding the forming alveole¹⁰¹. During the canalicular phase, two kinds of mechanical forces affect the developing lungs: one is the transpulmonary pressure, built up by the permanent secretion of lung fluid, and the other is cyclic stretch, generated by fetal breathing movements¹⁰². Between 24 and 26 weeks, the structural maturation of the lung tissue reaches the saccular stage, a state that allows extremely preterm infants to survive with the aid of intensive neonatal care. Still, the biochemical lung maturation has just begun: differentiated type 2 alveocytes are beginning to produce surfactant¹⁰². Alveolar structures can be recognized histologically by a GA of 32 weeks, and are uniformly present at 36 weeks¹⁰³. However, 85% of the alveoli are formed after birth, with intense multiplication during the first 2 years of life¹⁰⁴.

There is a huge difference between the consequences of oligohydramnios before and after the onset of pulmonary maturation. Extreme and persistent mid-trimester oligohydramnios, prior to 22-24 weeks, before the saccular stage of lung development, leads to pulmonary hypoplasia. This poses a risk of perinatal mortality as high as 80%¹⁰⁵, and survivors often have to face chronic pulmonary morbidities. Additionally, there is an increased risk of cord compression, joint contractures, skeletal anomalies, growth delay and pregnancy loss¹⁰⁶. The proper management of these cases is still a great challenge for both the obstetrician and the pediatrician. Evidence is currently accumulating that suggests the better efficacy of new therapeutic procedures relative to conventional management.

Aims

Our aim was to determine the efficacy of frequently used processes (antepartum transabdominal amnioinfusion (APTA), amniopatch (AP) and conservative management) in the treatment of early onset (13-26 weeks) oligohydramnios. We compared the outcomes of the conservative approach with the results of invasive strategies.

Materials and methods

A systematic review and meta-analysis were conducted. Studies on the management of second and early third trimester (13-26 weeks of gestation) oligohydramnios were reviewed from 2000 to 2013 in the conservative management and the APTA group, and all the reported cases with AP were analyzed. In the pooled analysis, the χ^2 test and Student's t-test were applied. Statistical significance was defined at the two-sided $p = 0.05$ level.

Results

Nine studies in the APTA group, 12 studies in the AP group and 7 studies in the conservative management group were analyzed.

The expectant management delayed pregnancy by a mean latency of 11.8 days (range 0-163). Pulmonary hypoplasia developed in 31.8% in this group. The overall perinatal survival rate following expectant management was 29.3%, while deformation defects occurred in 53%. The sum of the analyzed studies with conservative treatment is shown in Table 4. In the APTA group, the latency was significantly longer, at 37.4 days ($p < 0.001$). Pulmonary hypoplasia developed in 23.3%, although chronic lung diseases complicated the neonatal period in 34.8%. The overall perinatal survival was 49.1%, and the deformation defects were reduced to 36.5% ($p < 0.05$) by APTA. Severe maternal complications such as infection or placental abruption occurred in 22.4%. After AP, the pregnancy was delayed by 44 days ($p < 0.001$). The rates of both pulmonary hypoplasia and chronic lung diseases were below 1%. The perinatal survival was 61.4%. Postural deformity was not recorded among the AP survivors. The rate of procedure-related maternal complications was 28.2%, but serious complications such as infection or placental abruption occurred in only 8.3%. Tables 5 and 6 present an overview of the outcomes of APTA and AP. The results are compared in Figure 2.

Table 4. Conservative management of severe oligohydramnios in the second and early third trimester (13-26 weeks)

Study	Study population	Gestational age at oligohydramnios (weeks, mean and range)	Latency (days, mean, range or SD)	Fetal death / Neonatal death / Survival (%)	Pulmonary hypoplasia (% of liveborns)	Chronic lung disease (% of survivors)	RDS (% of survivors)	Sepsis (% of survivors)	Deformities (% of liveborns)	Intracranial hemorrhage/ leukomalacia (% of survivors)	Late neurological complications (% of survivors)
Pristauz et al. (2008) ¹⁰⁷	sPPROM n = 63 (71 fetus)	21.4 (14.0-24.9)	13 (0-118)	65/ 18/ 17	not given	25	17	42	not given	25	33.3
Falk et al. (2004) ¹⁰⁸	sPPROM n = 57 (79 fetus)	20.3 (14.0-23.0)	6 (1-161)	52.6/ 21.1/ 26.3	11.1	60	not given	11.1	7.4	n.g.	9.5
Williams et al. (2009) ¹⁰⁹	sPPROM n = 23	not given (18.0-24.9)	not given (5-84)	26.0/ 17.4/ 56.6	64.3	36	35.7	7.1	53.3	7.1	not given
Chauleur et al. (2009) ¹¹⁰	sPPROM n = 12 (13 fetus)	21.3 (15.0-23.9)	23.5 (1-94)	54/ 23/ 23	66.7	0	100	0	16.7	16.7	33.3
	iPPROM n = 13 (16 fetus)	19.6 (16.0-23.7)	43 (1-163)	31.2/ 0/ 68,8	27.3	0.9	54.5	0.9	27.3	36.4	18.2
Borgida et al. (2000) ¹¹¹	sPPROM n = 11	17.6 (15.6-19.6)	28 (±46)	82/ 9/ 9	not given	not given	not given	not given	not given	not given	not given
	iPPROM n = 11	16.4 (14.6-18.1)	124 (±48)	9/ 0/ 91	not given	not given	not given	not given	not given	not given	not given
Dinsmoor et al. (2004) ¹¹²	sPPROM n = 43 (57 fetus)	22.6 (16.9-24.0)	13 (0-96)	38.6/ 14/ 47.4	not given	29.6	83 (of liveborns)	34 (of liveborns)	not given	7.1	not given
Verma et al. (2006) ¹¹³	sPPROM n = 66	not given (18.0-23.0)	2.6 (0.5-27.2)	69.7/ 10.6/ 19.7	not given	69.2	61.5%	38.5	not given	46.1	38.5

RDS: respiratory distress syndrome; sPPROM: spontaneous preterm premature rupture of membranes; iPPROM: iatrogenic preterm premature rupture of membranes; SD: standard deviation

Table 5. Antepartum transabdominal amnioinfusion in severe oligohydramnios in the second and early third trimester (13-26 weeks)

Study	Study population	Intervention type	Gestational age at oligohydramnios (weeks, median and range)	Latency (days, mean, range)	Fetal death / Neonatal death / Survival (%)	Pulmonary hypoplasia (% of liveborns)	Chronic lung disease (% of survivors)	RDS (% of survivors)	Sepsis (% of survivors)	Deformities (% of liveborns)	Intracranial hemorrhage/ leukomalacia (% of survivors)	Late neurological complications (% of survivors)
Locatelli et al. (2000) ¹¹⁴	sPPROM n = 32 iPPROM n = 4	single = 11	16.5 (14.0-21.0)	89 (48-139)	0/27/73	10	not given	not given	not given	18	not given	0
		serial = 25	19.3 (14.0-25.2)	22 (9-105)	32/48/20	62	not given	not given	not given	16	not given	60
Ogunyemi et al. (2002) ¹¹⁵	sPPROM n = 11	single = 4 serial = 7	21.0 (15.0-24.0)	35.4 (3-83)	9.1/36.4/ 54.5	10	not given	not given	27.3 (of liveborns)	27.3	not given	not given
Tan et al. (2003) ¹¹⁶	sPPROM n = 6	single = 4 serial = 2	19.3 (16.0-25.0)	67.7 (14-126)	0/33.3/ 66.7	33.3	33.3	16.7	not given	not given	not given	0
De Santis et al. (2003) ¹¹⁷	sPPROM n = 29 iPPROM n = 8	single = 5 serial = 32	(mean \pm SD) 20.1 \pm 2.8	(mean \pm SD) 41.6 \pm 29.7	35.2/ 37.8/27	20.8	22.2	not given	16.6	16.6	not given	20
Stefos et al. (2005) ¹¹⁸	iPPROM n = 2	serial = 2	16.3 and 16.4	140	0/0/100	0	0	0	0	0	0	0
Hsu et al. (2007) ¹¹⁹	iPPROM n = 1 sPPROM n = 2 Idiopathic n = 8	single = 8 serial = 3	21.0 (19.0-25.0)	9.3 (7-14)	45.5/ 0/ 54.5	16.7	not given	not given	not given	not given	not given	not given
Kozinszky et al. (2013) ¹²⁰	Idiopathic n = 17	single = 11 serial = 6	21.6 (16.0-25.0)	28.4 (0-121)	58.8/ 5.9/ 35.3	0	14.2	42.8	14.2 (of liveborns)	14.2	0	0
Agressive treatment												
Chen et al. (2005) ¹²¹	sPPROM n = 4 Idiopathic n = 7	serial = 11 amniopatch = 1	23.3 (17.4-26.0)	34 (11-59)	10/10/80	not given	not given	not given	not given	not given	not given	not given
Miyazaki et al. (2012) ¹²²	sPPROM n = 45	serial = 45	22 (15-22)	24 (0-103)	15.6/24. 4/60	13.2	83.3	34.2 (of liveborns)	7.9	0	34.3	33.3

RDS: respiratory distress syndrome ; sPPROM: spontaneous preterm premature rupture of membranes; iPPROM: iatrogenic preterm premature rupture of membranes; SD: standard deviation

Table 6. Amniopatch in severe oligohydramnios in the second and early third trimester (13-26 weeks)

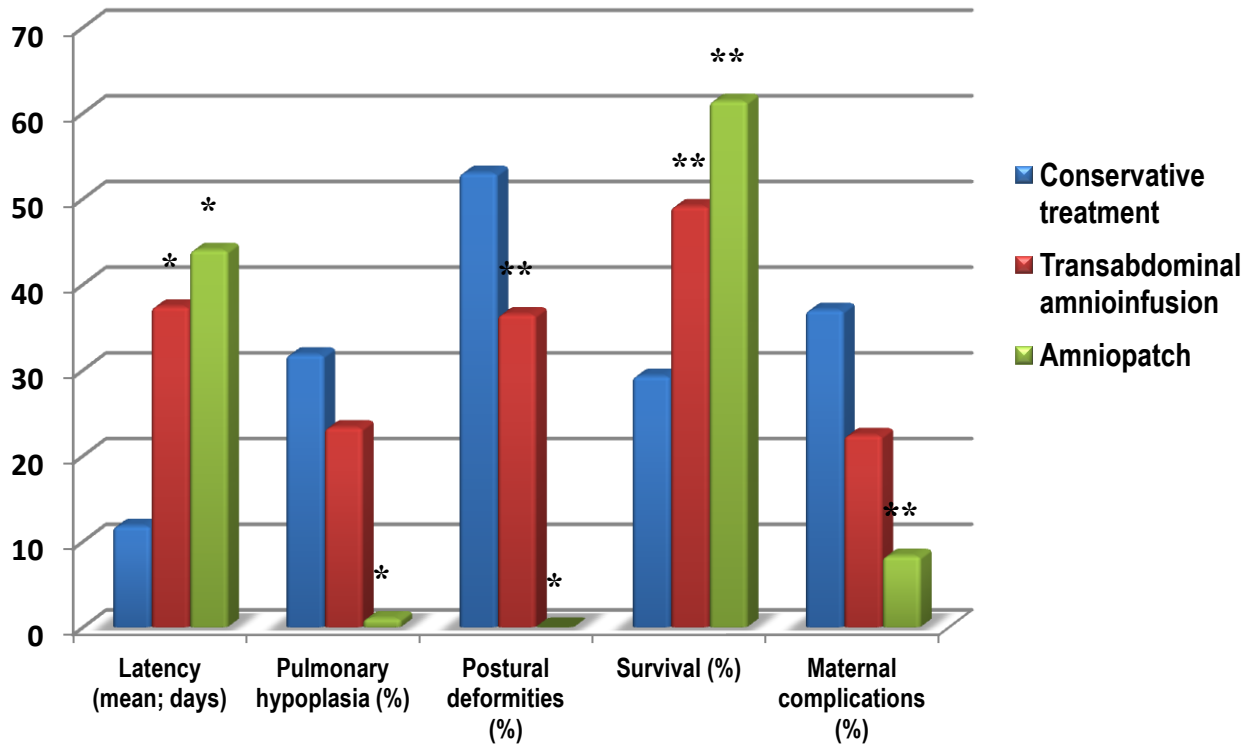
Study	Study population	Gestational age at oligohydramnios (weeks, median and range)	Latency (days, mean, range)	Fetal death / Neonatal death / Survival (%)	Pulmonary hypoplasia (% of liveborns)	Chronic lung disease (% of survivors)	RDS (% of survivors)	Sepsis (% of survivors)	Deformities (% of liveborns)	Intracranial hemorrhage/ leukomalacia (% of survivors)	Late neurological complications (% of survivors)
Sener et al. (1997)¹²³	iPPROM n = 1 (after TAAC)	16.1	147	0/0/100	0	0	0	0	0	0	0
Quintero et al. (2003)¹²⁴	iPPROM n = 26 (39 fetuses) (9 after TAAC, 1 after TA-CVS, 16 after fetoscopy)	18.7 (13.1-23.3)	75.6 (2-178)	30.8/5.1/64.1	0	not given	not given	2.6	0	0	0
Young et al. (2004)¹²⁵	sPPROM n = 4	16.4 (14.4-20.7)	21.5 (0-83)	75/0/25	0	100	100	0	0	0	0
	iPPROM n = 4	17.3 (15.4-20.7)	46.0 (2-89)	25/0/75	0	0	33.3	0	0	0	0
Contino et al. (2004)¹²⁶	iPPROM n = 3 sPPROM n = 2	19 (17-23)	68.6 (21-168)	20/0/80	0	0	not given	not given	not given	25	25
Lewi et al. (2004)¹²⁷	iPPROM n = 2 (3 fetuses) (after fetoscopy)	19.6 (17.2-22.0)	77 and 56	33.3/0/66.4	0	0	50	50	0	0	0
Sipurzynski-Budrass et al. (2006)¹²⁸	iPPROM n = 1 (after TAAC)	20	70	0/0/100	0	0	0	0	0	0	0
Cobo et al. (2007)¹²⁹	iPPROM (n = 5) (after TA-CVS)	13.3 (11.2-15.0)	19.4 (1-98.7)	80/0/20	0	0	0	0	0	0	0
Mandelbrot et al. (2009)¹³⁰	iPPROM n = 1 (after TAAC)	15.3	140	0/0/100	0	0	0	0	0	0	0
Pathak et al. (2010)¹³¹	iPPROM n = 3 (5 fetuses) (after fetoscopy)	21.7 (18.3-23.7)	95 (45-139)	20/0/80	0	0	25	0	0	0	0

Table 6. (continued) Amniopatch in severe oligohydramnios in the second and early third trimester (13-26 weeks)

Study	Study population	Gestational age at oligohydramnios (weeks, median and range)	Latency (days, mean, range)	Fetal death / Neonatal death / Survival (%)	Pulmonary hypoplasia (% of liveborns)	Chronic lung disease (% of survivors)	RDS (% of survivors)	Sepsis (% of survivors)	Deformities (% of liveborns)	Intracranial hemorrhage/ leukomalacia (% of survivors)	Late neurological complications (% of survivors)
Ferianec et al. (2011)¹³²	sPPROM n = 1	19.1	84	0/0/100	0	0	not given	not given	not given	not given	0
Kwak et al. (2013)¹³³	sPPROM n = 7 (8 fetuses)	21.0 (17.3-23.0)	46.5 (4-152)	12.5/ 12.5/ 75	0	71.4 (of liveborns)	71.4 (of liveborns)	57.2 (of liveborns)	not given	0	16.7
Richter et al. (2013)¹³⁴	iPPROM n = 13 (13 fetuses) (after needle-based procedure)	16.3 (15.2-19.0)	38.5 (0-101)	53.8/ 15.4/ 30.8	16.7	25	not given	not given	not given	not given	25
	iPPROM n = 11 (18 fetuses) (after fetoscopy)	20.2 (15.6-25.3)	58.8 (8-120)	16.7/ 11.1/ 72.2	0	0	not given	not given	not given	not given	7.7

RDS: respiratory distress syndrome; sPPROM: spontaneous preterm premature rupture of membranes; iPPROM: iatrogenic preterm premature rupture of membranes; TAAC: transabdominal amniocentesis; TA-CVS: transabdominal chorion villous sampling

Figure 2. Outcomes of three management strategies in cases of second and early third trimester (13-26 weeks) oligohydramnios



*: $p < 0.001$ and **: $p < 0.05$ compared to conservative management

Discussion

In our study, we aimed to analyze the latest perinatal results in midtrimester oligohydramnios management, since the improvement of neonatal intensive care units has an outstanding impact on the perinatal outcome. Due to the advances in obstetrical and neonatal care, a marked increase in neonatal survival has occurred during recent decades. The survival of very low birthweight (501-1000 g) infants improved from below 10% in 1959 to over 60% in 2009¹³⁵. However, the prognosis of midtrimester oligohydramnios is still poor. Besides the fetal malformations, PPRM is the most frequent cause of a decreased AFV in this period of gestation. The traditional obstetric management includes the administration of tocolytics and antibiotics to prolong latency and steroid administration to enhance pulmonary maturity¹³⁶. Miyazaki et al.¹²² demonstrated amniotic sac inflammation via histopathology in 91% of women with PPRM and in more than one-third of the cases clinical signs of chorioamnionitis appear¹³⁷. Broad-spectrum antibiotic treatment results in a lower frequency of chorioamnionitis and improved fetal survival as compared with patients without antibiotic administration¹³⁸. On the basis of these data, the use of

antibiotics has increased up to 97% in cases with PPROM¹³⁹. However, it is noteworthy that intra-amniotic inflammation can merely be controlled, and not eradicated with antibiotic therapy: subclinical chorioamnionitis remains despite the treatment¹²². The use of tocolysis is controversial, though a moderate effect on the latency period is suspected^{138,140}. Antenatal corticosteroid administration seems to improve the neonatal survival rate significantly¹³⁸ and it is recommended when viability has been reached. In the conservative treatment group, we demonstrated a mean latency of only 11.8 days from rupture of the membranes until delivery. 73% of the pregnancies ended within 2 weeks after rupture of the membranes. In the majority of the cases, the fetus could not reach the limit of viability during this short period, so conservative management resulted in less than a 30% survival rate. As regards pulmonary hypoplasia, the gold standard for diagnosis below 28 weeks of gestation is the post-mortem findings of a pulmonary weight to body weight ratio of < 0.015 (1.5%)¹⁴¹, though age-matched reference values can identify discrete, but potentially critical degrees of pulmonary underdevelopment more sensitively¹⁴². In our analysis, pulmonary hypoplasia was present in at least 31.8% of the liveborns, and the most important prognostic factors were the residual AFV and the GA before delivery^{137,151}. If oligohydramnios does not develop, the neonatal survival rate reaches 92% despite PPROM¹¹⁴.

APTA is the method that has been addressed as a technique for the restoration of a normal AFV, in order to prolong gestation and to prevent fetal complications at least until pulmonary maturity is achieved^{120,122,143}. The technical equipment is similar to that used for amniocentesis; it is performed with¹⁴⁴ or without local anesthesia¹²⁰, usually with a 20-22-gauge 150-mm amniocentesis needle, which is introduced^{116,120,144} transabdominally into the widest amnion pocket with the assistance of real-time ultrasonographic guidance^{114,145}. The infused crystalloids are 0.9% saline solution or Ringer's lactate solution at body temperature, which are both isotonic and do not induce any electrolyte imbalance in the fetus¹⁴⁶. The infused volume should depend on the GA and the amount of AF remaining inside the amniotic cavity^{144,147}. Our analysis demonstrated that the survival increases to 49.1%, which is a significant improvement as compared to expectant management. This encouraging result can be derived from the significant increase in latency time and a slight reduction in the rate of pulmonary hypoplasia due to the restored AFV. The survival rate for infants born alive increases progressively from 26% at 23 weeks to 84% at 26 weeks¹⁴⁸, and prolongation of the pregnancy is therefore of paramount importance. Some authors waited several days from the onset of AF leakage until the first APTA^{114,117,119}. The rate of spontaneous resealing is only 6-11%^{149,150}, while the risk of infection is high, and there is therefore no support for this 4-7 day delay until the first procedure. The extent of fluid loss after APTA has an impact on the success

of the treatment. De Santis et al. demonstrated that fluid loss occurred within 6 h after APTA in 100% of the neonates with pulmonary hypoplasia, as compared to 31.6% of the cases without¹¹⁷. If persistent oligohydramnios (deepest pocket of fluid 2 cm or less) requires serial APTA, lower neonatal survival and higher rates of pulmonary hypoplasia can be expected^{114,151,152}. In this group, oligohydramnios recurs within 1-48 h after treatment¹⁵¹. In view of this phenomenon, some authors suggest a test APTA to select appropriate cases of second and early third trimester PPROM for repeated APTA¹¹⁶. If the initial fluid is retained, the patient may benefit from serial treatment. In contrast with patients with ruptured membranes, serial APTA seems to be beneficial over a single procedure in cases of oligohydramnios with intact membranes. In our study population, serial procedures provided a longer latency period (repeated APTA: 69 days vs. single APTA: 10 days; $p = 0.002$) and delivery at a higher GA¹²⁰. Although membrane rupture occurring before and at the limits of viability complicates less than 1% of all pregnancies¹⁵³, infants who die as a result of preterm birth are born overwhelmingly at previable or periviable GAs¹⁵⁴. As a consequence, an „aggressive” management of PPROM was introduced^{121,122}. Within the framework of the treatment, patients are given hospital bed rest, and the administration of antibiotics and tocolytic drugs. Emergency cerclage is performed and serial APTA is applied through an indwelling catheter until delivery. The maternal and fetal status are closely monitored for the development of chorioamnionitis, labor and/or fetal compromise¹²². With this aggressive approach, a survival rate of 60-80% can be attained^{121,122}, but the proportion of chronic lung diseases and late neurological complications are relatively high (83.3% and 33.3%) among survivors¹²².

The use of invasive prenatal diagnosis and fetal surgery has increased during recent years. iPPROM remains one of the most common complications. The risk of fluid leakage after a simple needle procedure is around 1.7%¹⁵⁵, with sustained oligohydramnios reported in 0.3%¹⁵⁶. Biochemical leakage is much more frequent, but usually without any clinical consequences¹⁵⁷. Most pregnancies with iPPROM after amniocentesis will show the cessation of leakage and restoration of the normal AFV¹¹¹. After a fetoscopic procedure, iPPROM occurs in 5-30%, depending on factors such as trocar size and surgical duration¹⁵⁸. The use of AP is an accepted novel technique to achieve artificial membrane sealing following iatrogenic AF leakage. The method was first introduced after spinal anesthesia as an epidural blood patch¹⁵⁹, and it was first used to control postamniocentesis amniorrhea in 1997 by Sener et al.¹²³. During the procedure, warm isotonic saline (50-200 ml, optionally mixed with antibiotics) is infused intra-amniotically under ultrasonographic monitoring without knowledge of the exact site of rupture of the amniotic membranes. Cross-matched allogenic platelets [20-40 ml (0.5 units)] are infused, followed by 0.5 units of cryoprecipitate (including

clotting factors). Another 100 ml of normal saline is then instilled to achieve the optimal (> 5 cm) deepest pocket of the AF bag. Theoretically, the platelet/cryoprecipitate plug may seal the amniotic membranous defect by artificial platelet activation and fibrin adhesion at the site of the rupture, forming a 'white' coagulum as a plug^{123,124,126,133}. In our analysis, the overall perinatal survival rate was highest (61.4%) after treatment with AP. Although the amniotic leakage relapsed in 50.7%, the GA achieved at delivery (median 29.4 weeks) was significant. This technique is basically performed in the case of iPPROM. In sPPROM cases, the AP predominantly fails, usually because of infection¹³³. The membrane defects after needle-based procedures or fetoscopy are usually well demarcated and relatively small, and the needles or trocars are usually inserted into the uterine cavity under sterile circumstances. The membrane defects after sPPROM are mostly large, poorly delineated, over or near the internal cervical os, and commonly associated with intra-amniotic infections^{124,160}.

About 37% of patients with conservative treatment of midtrimester rupture of the membranes will have clinical signs of chorioamnionitis. Our analysis revealed that, compared with this, both the APTA and the AP technique had a lower complication rate. Severe maternal adverse events (infection or placental abruption) occurred in 22.4% of the APTA cases, and in only 8.3% in the AP group.

To date, 26 cases have been reported with AP treatment in cases of sPPROM. The procedure was successful in only 3 cases (11.5%)^{124-126,132,133}. This low success rate limits the use of AP for the treatment of iatrogenic amniotic leakage, and PPROM is rather a therapeutic target for APTA^{124,133,151,161}.

Despite the encouraging results of the active management of PPROM in the second and early third trimester, the patients are still in need of accurate information regarding the neonatal outcome and the risk of the intervention. Our analysis demonstrated that 25.8% of the patients opted for termination instead of APTA, and 15% preferred the termination of pregnancy in the AP group.

Management of severe idiopathic oligohydramnios with antepartum transabdominal amnioinfusion

Introduction

We have demonstrated that the second major factor contributing to fetal death was the presence of oligohydramnios¹⁶², but the exact role of oligohydramnios in third trimester fetal loss is still unclear^{55,57-59,62-65,68,69}. APTA has been proven to be an acceptable treatment option for the prevention of fetal complications in both the second and third trimesters^{97,163}. The AFV is artificially increased by the injection of normal saline or Ringer lactate solution transabdominally or transcervically into the amniotic cavity. The infusion of 250 ml of fluid is believed to increase the AFI by 4 cm^{147,164}. Augmenting the AFV may decrease the associated risk of oligohydramnios and increase the perinatal survival^{97,144,163}. The procedure can also be used as a diagnostic tool¹⁶⁵.

Aims

The objectives of the present observational study were to evaluate the outcome of pregnancies complicated by severe idiopathic oligohydramnios that were managed by APTA in the second or third trimester, and to identify the possible pregnancy complications related to the procedure. The maternal complications were also determined.

Materials and methods

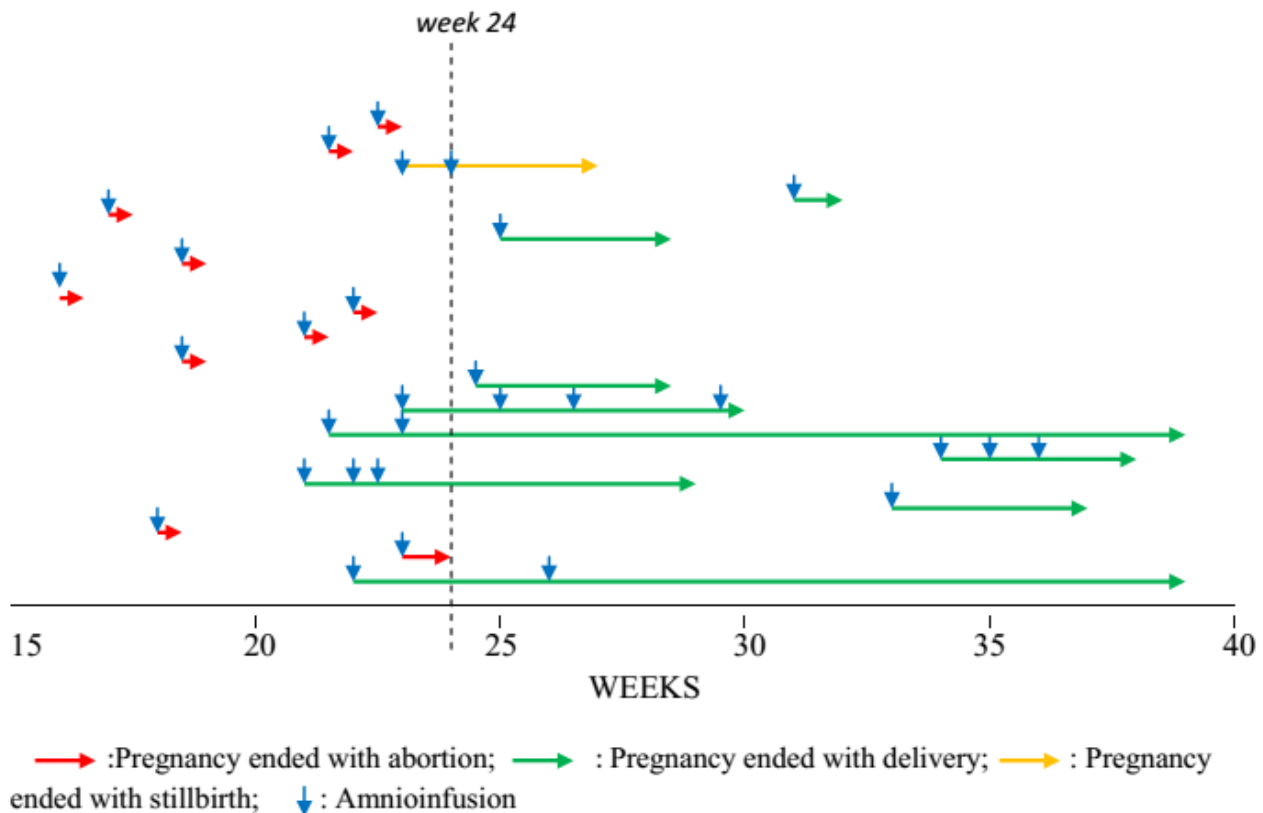
We performed our study on patients presenting at the fetomaternal unit of the Department of Obstetrics and Gynecology, University of Szeged, Hungary, with severe idiopathic oligohydramnios (AFI < 5 cm) during the period between December 2009 and January 2012. All possible cases with severe idiopathic oligohydramnios were enrolled into the study. The patients were in either the second or the third trimester, and the aim was prolongation of the gestation. Inclusion criteria were as follows: a) < 34 weeks of gestation; b) a singleton pregnancy; c) no PPRM; d) no symptoms indicative of incomplete abortion before 24 weeks of gestation; e) no active labor (< 3 cm of cervical dilatation; < 2 uterine contractions every 10 min) after 24 weeks of gestation; f) no clear signs of maternal or fetal infection (maternal tachycardia > 100/min, maternal temperature > 38°C, maternal white blood cell count > 15,000/ml, maternal C-reactive protein > 20 mg/l, uterine tenderness, a foul-smelling vaginal discharge, fetal tachycardia > 160 bpm); and g) no suspicion of placental abruption (uterine tenderness and “unexplained” bleeding episodes). We

excluded from the study women with pregnancies complicated by lethal congenital abnormalities and women who declined after giving their informed consent. At presentation, all the women were examined to exclude rupture of the membranes (vaginal AF loss)¹⁶⁶. The GA was confirmed on the basis of a first-trimester ultrasonographic examination. The AF was assessed by using the AFI with the sum of the four quadrants maximum pockets of AF⁵². Severe oligohydramnios was diagnosed when the AFI was < 5 cm irrespective of the pregnancy duration, and APTA was performed without delay. All APTA procedures were performed by the same experienced sonographer. Under sterile circumstances, without sedation, a Chiba 20® 150-mm needle (Neomed Corporations, Debrecen, Hungary) was introduced transabdominally into the amniotic cavity, into the widest pocket of the amnion, under ultrasonographic guidance (Kretz Sonoace 8000, Voluson 730Pro). A variable volume of 37 °C saline solution (0.9% NaCl, 180-900 ml) was infused transabdominally into the amniotic cavity under continuous ultrasonographic control. The infusion of 250 ml of fluid is believed to increase the AFI by 4 cm^{147,164}, but saline solution was infused until a normal amount of fluid was restored exceeding the upper limit of moderate oligohydramnios (AFI = 5-8 cm)⁴⁷. After this, an ultrasonographic fetal morphological evaluation was carried out by the same examiner. The fetal biometric parameters, the heart rate before and after the procedure, the location of the placenta (anterior, posterior or lateral), and the amount and the duration of the APTA were recorded. Prophylactic antibiotic therapy was not administered in any of the cases. The vaginal leakage of fluid was monitored continuously by the patient herself. The patients were followed up weekly for repeated AFI measurement in order to assess the need for further infusions (AFI < 5 cm). In the event of a lethal malformation of the fetus, termination of the pregnancy was offered to the patient. After the filling of the amniotic cavity, lethal abnormalities (bilateral renal agenesis) were noticed in 4 cases, which were excluded from the statistical analysis. Karyotyping from the sample during this procedure revealed only negative results in all of the included cases. A repeat ultrasonographic examination was carried out within 24 h after the procedure in order to control recurrence or PPRM. In cases of ongoing pregnancy, ultrasonography was performed weekly to assess the need for further infusion (AFI decreased below 5 cm again). Statistical analysis was performed with the SPSS for Windows program (SPSS 15.0, Inc. Chicago, IL, USA). Comparisons were assessed by the Kruskal-Wallis test for continuous variables. χ^2 analysis with the Yates correction when necessary, or the Fisher exact test was used to test differences in proportions. A confidence level of $p < 0.05$ was taken to indicate statistical significance. Formal confirmation that ethical approval was not required for this observational study was obtained.

Results

Altogether 20 cases fulfilled the criteria for enrollment. The mean GA at the time of the initial APTA was 22.6 weeks (range: 16.0-33.9 weeks). The mean number of infusions was 1.5 per pregnancy. APTA due to recurrent oligohydramnios was performed once in 14 pregnancies, twice in 3 pregnancies, 3 times in 2 pregnancies and 4 times in 1 pregnancy. Thus, a total of 30 APTAs were performed. The procedures were mostly repeated weekly in serial cases. The duration of pregnancy at the time APTA was performed was < 24 weeks in 70% of the patients; and < 33 weeks in 25%. Ten amnioinfusions were complicated by spontaneous abortion (50.0%) (started by vaginal AF loss, followed by uterine activity within 3 days from the procedure) and one intervention was followed by intrauterine fetal demise (5.0%; 1/20). Most of the single procedures (71.4%, mean GA: 19.4 weeks) were carried out in the second trimester, but all single APTA processes at that stage resulted in spontaneous abortion after a short latency period (mean: 4 days; range: 0-14 days). The vast majority of repeated procedures were also started in the second trimester (83.3%), with the exception of the case where the oligohydramnios was detected at 33 weeks of gestation, and 3 series of APTA were given. The interval between the first infusion and the spontaneous abortion/delivery (latency period) was 27.6 ± 37.2 days. Serial procedures led to delivery at a higher gestational age than the single procedures (latency period: $p = 0.002$; repeated: 69 days vs single: 10 days). For patients with a GA between 16 and 24 weeks, the latency period ranged from 1 to 121 days. The mean latency period for this interval was 30 days. For the women with a pregnancy duration between 25 and 28 weeks, the mean latency period was 7 days; for those with a GA of >28 weeks, the mean latency period was 29 days. A schematic overview of the study cases is presented in Figure 3. The clinical characteristics of the pregnancies of the women undergoing spontaneous abortion and delivery are displayed in Table 7. (One case was excluded where a procedure was performed twice from weeks 23 of gestation, but the pregnancy resulted in intrauterine fetal demise and the induction of labor was performed.)

Figure 3. Schematic overview of gestational age at amnioinfusion procedures, latency periods and pregnancy outcomes in study cases with severe oligohydramnios



In 7 of the pregnancies below 24 weeks of gestation, PPROM developed after APTA and spontaneous abortion occurred within 3 days after the procedure. In 4 of these 7 cases, retroamniotic filling of saline solution and a floating amniotic membrane were observed immediately after the start of the procedure following introduction of the needle into the insertion site (Figure 4). Retroamniotic filling with approximately 20-30 ml of administered saline went on to develop rupture of the membranes (vaginal AF loss) within 48 h of the APTA in every case. One woman with a 19-week pregnancy developed chorioamnionitis within 24 h after APTA despite the fact that there were no clinical signs of spontaneous abortion preprocedure, such as maternal fever, uterine activity or bleeding. Microbiological examination revealed *Mycoplasma* infection. However, in terms of perioperative complications of the deliveries, there was only one case of PPROM within 24 h of the APTA, but this pregnancy continued until premature delivery at 28.3 weeks of gestation. (In another case, we started to inject the saline infusion into the fetal abdominal cavity by accident; the needle was removed to the amniotic cavity immediately and the procedure was continued with no fetal complication. The fetal intra-abdominal fluid was absorbed within 24 h, but delivery could be prolonged by only 14 days due to rupture of the membranes leading to delivery.)

Table 7. Pregnancy characteristics in severe oligohydramnios cases treated with transabdominal amnioinfusion

	Pregnancy followed by delivery (n = 9)		Procedure-related spontaneous abortion (n = 10)		p value	OR (95% CI)
	n	%	n	%		
Maternal age (years) (mean±S.D.)	32.7 ± 4.6		30.1 ± 8.0		n.s.	
Primigravidity	1	11.1	4	40	n.s.	0.14 (0.01-1.76)
Previous cesarean section	3	33.3	0	0	n.s.	1.6 (0.93-2.74)
Oligohydramnios in previous pregnancy	0	0	0	0		
Major congenital malformation in previous pregnancy	1	11.1	1	10	n.s.	1.0 (0.05-19.4)
Posterior placenta location	6	66.7	6	60	n.s.	1.3 (0.20-8.71)
Gestational age at spontaneous abortion / delivery (mean weeks) (range)	33.1 (28-39.1)		20.3 (17-23.9)			
Premature birth	5	55.6	-	-		
Preterm premature rupture of membranes	2	22.2	7	70	0.07	0.12 (0.01-0.98)
Retroamniotic filling	-	-	4	40		
Placental abruption	3	33.3	-	-		
Intrauterine growth retardation	2	22.2	-	-		

Statistical comparisons were performed with the Mann-Whitney U test test and the Fisher exact test for continuous and categorical variables, respectively; S.D.: standard deviation; n.s.: statistically not significant; OR: odds ratio; 95% CI: 95% confidence interval;

Women who delivered after APTA were at a more advanced age than those whose pregnancies were followed by spontaneous abortion, but without any significant difference. The rates of primigravidity and previous CS did not differ statistically significantly between the two groups. The two groups were also similar in terms of the number of previous deliveries. Interestingly, no case of oligohydramnios had been recorded in the previous pregnancies. The rates of congenital abnormalities in the previous pregnancies were very low in both groups. There was no report of any hypertension prior to or during pregnancy in any of the cases. No other maternal complication was present in any of the pregnancies. In 4 cases, delivery occurred at term, whereas more than half of the deliveries (5 cases) took place prematurely.

Figure 4. Retroamniotic filling immediately after the start of amnioinfusion



Four (44.4%) had a normal vaginal delivery, while 5 (55.6%) underwent a CS. Perinatal complications in liveborn cases are listed in Table 8. The APTA procedures were successful and uneventful in 78.6% of the pregnant women in terms of fetal complications; however, temporary fetal bradycardia was observed in 3 cases during the procedure. No maternal intraprocedural complications were recorded. One neonatal death occurred, in a case when APTA was followed by PPRM after a 5-week period, and delivery at 28.3 weeks of gestation. Perinatal death occurred on the fourth postpartum day, due to *Pseudomonas* infection. None of the neonates presented external lesions due to the APTA procedures. Table 9 compares the APTA-related characteristics in the two groups. The GA at the initial APTA was similar in the two groups, but the latency period was longer in the pregnancies that were followed by deliveries. The women who underwent spontaneous abortion received a single APTA, whereas those who delivered received serial APTA more commonly, but with no significant difference. The overall mean amount of fluid infused was 397.3 ml (180-670 ml) (not presented in the Table).

Table 8. Times of intervention and delivery, and perinatal complications in liveborn cases treated with transabdominal amnioinfusion due to severe oligohydramnios

	GA at amnioinfusion (weeks)				GA at delivery	Neonate	Apgar score (at 1/5/10 min)	Perinatal complications
1	21.9	26.1			39.3	3230 g, female	9/10/10	-
2		33.3			37.3	2390 g, female	9/10/10	-
3	21.0	21.7	22.3		29.0	1350 g, male	4/4/7	preterm labor, RDS, foot deformity
4	33.9	34.7	35.7		38.0	2680 g, male	10/10/10	breech presentation, CS
5	21.6		23.4		38.9	3120 g, male	10/10/10	agenesis of left kidney, hypoplasia of right kidney
6	22.9	24.9	26.3	28.9	29.9	990 g, male	7/8/8	placental abruption, CS,
7		24.3			28.9	1200 g, female	3/6/6	preterm labor, breech presentation, CS, RDS, NEC
8		24.9			28.3	1340 g, male	7/7/7	placental abruption, CS, RDS, NEC, sepsis, neonatal death
9		30.7			31.7	1160 g, female	8/8/8	placental abruption, CS

GA: gestational age; CS: Cesarean section; RDS: respiratory distress syndrome; NEC: necrotizing enterocolitis

The amount of fluid infused at the first procedure was not significantly different in the two groups, whereas the overall mean volume was statistically significantly higher amongst those who delivered. Paradoxically, a higher amount of infused fluid posed a lower risk factor as concerns rupture of the amniotic membranes, but not significantly so. Pregnancies with PPROM [n = 7]: 340 ± 101 ml vs. pregnancies not complicated by PPROM [n = 9]: 433.1 ± 110 ml; $p < 0.05$. Serial APTA led to PPROM in only 1 case [not presented in the Table]. It is of note that there were no cases of fetal distress, and tocolytics were not administered to any patient as most of the preterm pregnancies presented with advanced labor (uterine contractions), and 1 case had chorioamnionitis for which immediate delivery was indicated. It is also important that there were no recorded cases of pulmonary hypoplasia.

Discussion

In our previous review, we demonstrated the benefit of APTA treatment in the event of PPROM in the second trimester¹⁶³. In contrast, there is currently a lack of evidence supporting this procedure amongst idiopathic cases of severe idiopathic oligohydramnios¹⁴⁴. Accordingly, our present investigation focused on selected cases with no obvious reason for severe oligohydramnios. As concerns the results, the prevalence of fetal loss (55%) was unexpectedly high.

Table 9. Procedure characteristics of pregnancies with severe oligohydramnios treated with transabdominal amnioinfusion. Comparison of cases resulted in delivery and spontaneous abortion.

	Pregnancy followed by delivery (n = 9)		Procedure-related spontaneous abortion (n = 10)		P value	OR (95% CI)
	n	%	n	%		
GA at first APTA (mean in weeks) (range)	25.3 (21.0-33.0)		20.0 (16.0-23.9)		n.s.	
Latency period (days) (mean)	54.4 ± 42.1		4.3 ± 4.4		0.001	0.44 (0.21-0.92)
Single procedure	4	44.4	10	100	n.s.	
Volume infused at first APTA (ml) (mean ± S.D.)	430.0 ± 132.2		340.0 ± 115.9		n.s.	
Volume infused at all APTAs (ml) (mean ± S.D.)	444.1 ± 93.6		308.9 ± 101.1		< 0.05	

Statistical comparisons were performed with the Mann-Whitney U test and the Fisher exact test for continuous and categorical variables, respectively. Latency period: interval from first infusion to abortion/delivery. GA: gestational age; APTA: antepartum transabdominal amnioinfusion; S.D.: standard deviation; n.s.: statistically not significant; OR: odds ratio; 95% CI: 95% confidence interval

This is basically a consequence of the high proportion of spontaneous abortion in the second trimester, which was mainly the result of the procedure-related rupture of the membranes (7 of 16 second trimester cases). These findings do not correlate with observations in other investigations^{97,167}. Chhabra et al. conducted a case-control study of 100 pregnant women with oligohydramnios⁹⁷. Although the amnioinfusion population included not only patients with severe, but also patients with moderate oligohydramnios, decreases in perinatal mortality (4% of study the group vs. 18% of the controls), postural deformities (0% in the study group and 4% in the controls) and the rate of CS (18% in the cases vs. 46% in the controls) were demonstrated. Gramellini et al.¹⁴⁴ achieved a significantly longer latency period in the group of women with oligohydramnios without PPRM (30 days vs. 9 days $p < 0.05$). In our experience, the pregnant women who developed spontaneous abortion revealed two very important characteristics: rapidly evolving PPRM and retroamniotic filling of the infused fluid. If APTA is followed by PPRM within a short time period (3 days) in the second trimester, then the risk of spontaneous abortion is fairly high. A possible underlying mechanism of action of the fulminant PPRM could be that the long-acting lower intrauterine pressure may lead to a damaged integrity of the amniotic membranes with a lower resistance during stretching during the continuously increasing pressure in the course of APTA. If rupture does not occur in the first 3 days, then the probability of the prolongation of gestation is significantly increased, but more than one procedure is typically required (62.5%) due to the recurrence of the oligohydramnios. As a special finding, we observed the retroamniotic filling of saline in 4 cases, suggesting the iatrogenic rupture of the membranes at the infusion site as a

major adverse technical complication of APTA. A floating amniotic membrane is visualized immediately after the instillation of fluid into the amniotic cavity in these cases. The 20-30 ml saline solution coming into contact with the uterine wall behind the amniotic membranes may induce uterine irritability and contractions. Retroamniotic filling of infused fluid between the amniotic membrane and the uterine wall may also lead to separation of the membrane from the uterine wall, resulting in vaginal leakage of the AF shortly after APTA in every case.

In the vast majority (75%) of the cases, the severe idiopathic oligohydramnios developed in the second trimester. Strong et al.¹⁶⁴ noted a 4-cm AFI increase following an intrauterine infusion of 250 ml of saline solution. The amount infused on a single occasion of APTA is usually lower than that in our study. In Chhabra's report, an infusion of 250 ml of saline solution caused a mean AFI increase of 4.02 cm⁹⁷, whereas others¹⁶⁸ described a mean increase in the SDP of 1.89 cm following a mean infused volume of 283 ml fluid, resulting in a 23.5% pregnancy loss rate. As compared with other studies^{97,144,164,168}, severe idiopathic oligohydramnios was treated with a significantly higher volume of infused fluid in our study (the mean amount of saline infused was 397.3 ml saline) with the idea of a not too frequent APTA for those pregnant women who have severe oligohydramnios, and the risk of spontaneous abortion or PPRM was higher. However, it is very controversial that a higher volume of saline infused into the amniotic cavity poses a lower risk of rupture. In other words, a higher initial AFI requires a lower amount of infused saline, which involves a higher probability of rupture of the membranes fairly rapidly. Nevertheless, it can be concluded that the earlier the severe idiopathic oligohydramnios develops, the higher the risk of rupture of the membranes and spontaneous abortion following APTA.

Although no maternal intraprocedural complications were recorded, the rate of placental abruption in our study group is noteworthy. We experienced placental abruption in 3 pregnancies (15%) within several days after the last APTA (mean: 12.7 days; range: 7-24 days). This proportion is in line with the 9-16.7% rate reported in the literature¹¹⁴⁻¹¹⁶. However, the APTA procedure does not seem to increase the risk of this complication, since a similar rate of placental abruption was found in the APTA cases to that in the cases without intervention (16.0 vs. 23%)¹¹⁴. This is supported by the fact that oligohydramnios has been shown to be an independent risk factor for placental abruption¹⁶⁹⁻¹⁷¹. If we consider the results of previous reports, the benefits of the procedure exceed the risk of spontaneous abortion¹⁶³. APTA decreases the rate of pulmonary hypoplasia as the most dangerous neonatal consequence of permanent oligohydramnios. In line with this observation, there was no case of pulmonary hypoplasia in our study population.

Summary

We conducted a retrospective analysis on the pregnancies complicated with third trimester intrauterine fetal death. Despite the outstanding autopsy rate, the proportion of unexplained stillbirths remained high. Maternal obesity, lack of adequate antenatal care and maternal hypertensive disorders were the most frequent maternal risk factors, while IUGR, oligohydramnios and fetal macrosomia were the most important fetal conditions. Our results underline the importance of antenatal care and effective screening for intrauterine growth disorders and oligohydramnios in the third trimester.

The proper management of oligohydramnios and PPROM in the second and early third trimester is still not sufficiently established. In a meta-analysis, we compared the results of conservative management with invasive approaches such as APTA and AP procedures. We demonstrated that the invasive approach increases the time until delivery, which is essential in improving the perinatal survival. Both invasive methods moderate the consequences of oligohydramnios such as pulmonary hypoplasia and postural deformities, while the occurrence of maternal complications also decreased. Our results indicate that APTA is a suitable method in the management of sPPROM, while AP is appropriate in the treatment of iPPROM.

We performed an observational study on pregnant treated with APTA because of severe idiopathic oligohydramnios ($AFI < 5$) between 16-34 weeks. In the majority of cases, the oligohydramnios developed in the second trimester. PPROM, active labor and chorioamnionitis were excluded. The mean prolongation of the pregnancies was almost 4 weeks, and especially serial procedures resulted in a longer latency time. As a new finding, an inverse correlation was found between the amount infused and the probability of PPROM. Immediate retroamniotic filling of saline solution after the start of the procedure with a floating amniotic membrane predicted spontaneous abortion within 48 h. Since procedure-related maternal complications were not observed, APTA is a suitable method for reducing oligohydramnios-related neonatal complications such as pulmonary hypoplasia or postural deformities.

Acknowledgments

I am indebted to my family for their love and patience. I thank my tutors, **Professor Attila Pál** and **Dr. Gábor Németh**, for their continuous support and advice. I am grateful to **Dr. János Sikovanyecz** and **Dr. Zoltán Kozinszky** for their invaluable help, to **Dr. József Daru**, **Dr. Attila Keresztúri**, **Professor György Bártfai** and **Professor János Szöllősi** for their support.

Blessed is the one
who does not walk in step with the wicked
or stand in the way that sinners take
or sit in the company of mockers,
but whose delight is in the law of the LORD,
and who meditates on his law day and night.
That person is like a tree planted by streams of water,
which yields its fruit in season
and whose leaf does not wither—
whatever they do prospers.

/Psalms 1:1-3/

A Doktori Értekezés magyar nyelvű összefoglalása

Bevezetés

A magzatvíz ideális környezetet biztosít a magzati növekedés számára. Védelmet nyújt a sérülések ellen, lehetőséget biztosít a magzatmozgásokhoz, amelyek alapvetőek a csont- és izomrendszer normál fejlődéséhez. A magzatvíz szerepet játszik a magzati metabolikus folyamatokban, meghatározott hőmérsékletet biztosít és esszenciális a tüdő egészséges fejlődése szempontjából is. Míg a magzatvíz összetételének szabályozása rendkívül szoros és rendellenességei ritkák, addig a magzatvíz mennyiségi eltérései jóval gyakrabban fordulnak elő. A magzati kultakaró szarusodását követően a magzatvíz körforgásában szerepet játszó tényezők jól meghatározottak és állatkísérletes adatok alapján javarészt ismertek.

A terhességek 4-4,9%-a jár kórosan csökkent magzatvíz mennyiséggel. Oligohydramnióknak definiáljuk a terhességi kornak megfelelő magzatvíz volumen 5 percentilis, vagy az alatti mennyiségét. A súlyos mértékű csökkenés alapvetően 6 fő okra vezethető vissza: 1) magzati fejlődési rendellenesség; 2) idő előtti burokrepedés; 3) izolált/idiopathiás forma; 4) lepényi elégtelenség; 5) többes terhességekben jelentkező szövődmény; 6) iatrogen. Az oligohydramnion leggyakrabban a 13-21 és a 34-42 terhességi hetek között jelentkezik. A klinikai gyakorlatban a magzatvíz mennyiségének becslése ultrahangvizsgálattal történik, a szubjektív megítélésen túl két számítási módszert használnak elterjedten: 1) magzatvíz-index, mely során a méh négy quadransában a magzatvíz-zsebek vertikális méretét összegzik; 2) legnagyobb magzatvíz-zseb: a legnagyobb magzatvíz-zseb vertikális átmérőjét mérik.

A harmadik trimeszterben jelentkező oligohydramnion esetén emelkedett a nem megnyugtató kardiotokográfiás regisztrátumok és a szülésindukciók gyakorisága. Ugyanígy gyakrabban fordul elő meconium aspiráció, az újszülött intenzív osztályon való ápolása, illetve emelkedett a perinatalis halálozás. Mindezek ellenére nem egyértelmű az összefüggés az alacsony köldökzsinórvér pH és a csökkent magzatvíz mennyiség között. Egyes vizsgálatok eredménye szerint az oligohydramnion csak a magzat méhen belüli növekedési retardációjával együtt jelentkezve jelent additív kockázatot, míg az izolált oligohydramnion nem emeli a perinatalis morbiditást.

A 24-26. terhességi hét előtt kialakult oligohydramnion jelentős kockázati tényező az újszülött pulmonalis hypoplasiája és a váz-izomrendszeri deformitások szempontjából. A

pulmonalis hypoplasia mortalitása eléri a 80%-ot. Mivel a megfelelő mennyiségű magzatvíz elengedhetetlen a tüdő egészséges fejlődéséhez, így feltételezhető, hogy a magzatvíz mennyiségének helyreállítása jótékony hatású a tüdőfejlődés szempontjából. A második trimeszterben és a korai harmadik trimeszterben jelentkező oligohydramnion sok esetben idő előtti burokrepedés kapcsán alakul ki, amely tovább rontja a prognózist.

Munkám fókuszában az oligohydramnion jelentőségének felmérése, illetve kezelésének lehetőségei álltak. Kutatásunk három fő részre osztható:

1. Harmadik trimeszter során intrauterin magzati elhalással szövődött terhességekben vizsgáltuk retrospektíven az oligohydramnion előfordulását, az anyai és magzati rizikófaktorok gyakoriságát, a magzat elhalásának okát, illetve megvizsgáltuk ezek kapcsolatát.
2. Az oligohydramnion kezelésére a nemzetközi gyakorlatban három eljárás elfogadott, úgymint konzervatív kezelés, transabdominalis amnioinfúzió és az amniopatch technika. Meta-analízist végeztünk és összehasonlítottuk a 13-26. terhességi hét között jelentkező oligohydramnion esetén ezeknek a kezelési módszereknek az eredményességét, különös tekintettel a perinatalis halálozás, a pulmonalis hypoplasia, valamint a végtagdeformitások előfordulására.
3. Saját beteganyagunkban megvizsgáltuk a transabdominalis amnioinfúzió eredményességét 16-34. gestatiós hét között jelentkező idiopathiás oligohydramnionnal szövődött terhességek esetén.

Az oligohydramnion és más rizikófaktorok vizsgálata harmadik trimeszteri intrauterin magzati elhalással szövődött terhességekben a foetopathologiai és lepény szövettani eredmények alapján

Anyag és módszer

1996-2010 között a Szegedi Tudományegyetem Szülészeti-Nőgyógyászati Klinikán lezajlott harmadik trimeszteri halvaszülések adatai kerültek retrospektív módon feldolgozásra. Vizsgáltuk az ismert rizikófaktorok előfordulását, valamint a magzat és a méhlepény szövettani eredményei alapján az elhalás lehetséges okát. A magzati elhalás okának meghatározásában a klinikai tényezők is figyelembe lettek véve.

Eredmények

A vizsgált 15 éves periódus alatt 29897 szülésből 140 halvaszülés történt (4,7‰), 126 esetben (90%) egyes terhességben, míg 14 esetben (10%) ikerterhességben. Az átlagos terhességi kor 31 hétnek adódott. Az anyai rizikófaktorok közül leggyakoribbnak az anyai elhízás (BMI > 30

kg/m²) (22,1%), a gondozatlan terhesség (20,7%), illetve a hypertóniával járó kórképek (19,3%) adódtak. Az adatokat az 1. táblázat (Table 1. – 13. oldal) szemlélteti. A magzat növekedési retardációja (47,8%), az oligohydramnion (10%), illetve az excesszív magzati növekedés (8,6%) voltak a leggyakoribb magzati rizikófaktorok. Az eredményeket a 2. táblázat (Table 2. – 13. oldal) mutatja be. Az ismeretlen eredetű magzati veszteség magas aránya (42,1%) mellett a leggyakoribb haláloknak a lepényi elégtelenség (27,1%) és a köldökszinór eredetű magzati elhalás (15,0%) bizonyult. Intrapartum magzati elhalás nem történt. Az adatok a 3. táblázatban (Table 3. - 14. oldal), illetve az 1. ábrán (Figure 1. – 15. oldal) láthatóak. Vizsgálatunkban az oligohydramnion és a magzat növekedési retardációjának előfordulása szignifikáns összefüggést mutatott. Az oligohydramnionnal jelentkező esetek 78,6%-ában intrauterin magzati növekedési elmaradás is igazolódott.

Megbeszélés

A harmadik trimeszterben bekövetkező magzati elhalás incidenciája fontos jellemzője a szülészeti tevékenységnek, mindemellett a perinatalis mortalitásban jelentős szereppel bír. Vizsgálatunkban az előfordulási gyakorisága 4,7%-nek adódott, amely megfelel a fejlett országokban tapasztaltaknak. A kiemelkedő szövettani vizsgálati arány (97,9%) ellenére a magzati elhalás aetiologiája jelentős hányadban (42,1%) ismeretlen maradt. Hasonlóképpen, más tanulmányokban az ismeretlen magzati veszteség előfordulása 23,2-66,2% között változik, de az oki csoportok felosztása nagymértékben függ az értékelés során alkalmazott klasszifikáció típusától.

Vizsgálati anyagunkban az oligohydramnion előfordulási gyakorisága duplája (10%) volt, mint amit populációs megfigyelések kapcsán közöltek. Az esetek közel négyötöde a magzat növekedési elmaradásával társult. A magzatvíz csökkent mennyiségének prediktív szerepe a magzati elhalás tekintetében továbbra sem egyértelmű. Chamberlain és munkatársai kutatásuk során a perinatalis mortalitás ötvenötszörös emelkedését figyelték meg oligohydramnion esetén. Chhabra és munkatársai anyagában a magas rizikójú terhességek 18%-a perinatalis veszteséggel végződött, amennyiben oligohydramnion volt jelen. A szakirodalmi adatok ismeretében a mi megfigyelésünk is alátámasztani látszik azt a véleményt, miszerint az oligohydramnion a magzati veszteség szempontjából akkor számít additív rizikótényezőnek, ha a magzat növekedési elmaradásával együtt jelentkezik

A második és korai harmadik (13-26 hét) trimeszterben jelentkező oligohydramnion kezelési lehetőségei

Anyag és módszer

A szakirodalom meta-analízisét végeztük annak meghatározására, hogy a jelenleg elfogadott három módszer (konzervatív kezelés, transabdominalis amnioinfúzió, amniopatch technika) közül melytől várható a legjobb eredmény a 13-26. terhességi hét között fellépő oligohydramnion kezelésében. A konzervatív kezelés és a transabdominalis amnioinfúziós csoportban a témával foglalkozó 2000 és 2013 között megjelent tanulmányokat, míg az amniopatch csoportban az összes eddig megjelent tanulmányt tekintettük át. Vizsgáltuk a terhesség prolongációjának idejét (latencia idő: kezelés kezdete és terhesség befejeződése közt eltelt idő), a perinatalis halálozást/túlélést, a pulmonalis hypoplasia, végtagi deformitások előfordulását, valamint a súlyos anyai szövődmények (sepsis, korai lepényleválás) gyakoriságát. Analízisünk során χ^2 - és Student t-tesztet alkalmaztunk, statisztikailag szignifikánsnak a $p \leq 0,05$ eredményt tekintettük.

Eredmények

A konzervatív kezelés csoportjában hét, a transabdominalis amnioinfúzió csoportjában kilenc, az amniopatch csoportban 12 tanulmányt analizáltunk. Az áttekintett publikációkat összefoglalva prezentálja a 4., 5. és 6. táblázat (Table 4. – 20. oldal, Table 5. - 21. oldal, Table 6. – 22 és 23. oldal). A konzervatív kezelés a terhességeket átlagosan 11,8 nappal prolongálta, ugyanez az időtartam 37,4 nap ($p < 0,001$) transabdominalis amnioinfúzió és 44 nap ($p < 0,001$) amniopatch technika alkalmazása kapcsán. A neonatalis túlélés 29,3%, 49,1%, 61,4% ($p < 0.05$) volt a konzervatív, amnioinfúziós és amniopatch technikával kezelt csoportokban. Az aktívan kezelt csoportokban a terhességek ideje szignifikánsan hosszabb volt a konzervatívan kezelt csoporthoz képest. Szintén jelentős csökkenés volt megfigyelhető a pulmonalis hypoplasia és a végtagi deformitások előfordulási gyakorisága, illetve az anyai komplikációk gyakorisága között. Az eredményeket a 2. ábra (Figure 2. – 24. oldal) prezentálja.

Megbeszélés

Vizsgálatunkban igyekeztünk a legfrissebb eredmények analízisére törekedni, mivel a neonatalis intenzív terápiás eszköztár rohamos fejlődése jelentősen befolyásolja a perinatalis mortalitási és morbiditása mutatókat. Ugyanakkor a 13-26. terhességi hét között jelentkező oligohydramnion prognózisa továbbra sem megnyugtató. A magzati fejlődési rendellenességhez társuló eseteket nem

számítva, ebben a terhességi korban az oligohydramnion egyik leggyakoribb oka az idő előtti burokrepedés. A konzervatív megközelítés alapja az antibiotikum és tocolyticus kezelés a terhesség prolongálása érdekében, majd kortikoszteroidok alkalmazása a tüdő érésének gyorsítására. Ugyanakkor vizsgálatunk alapján konzervatív kezeléssel ebben a gestatiós korban szerény eredmények érhetőek el, a terhességek 73%-a magzatburok megrepedését követő 2 héten belül befejeződik. Ez a latencia idő rendszerint nem elegendő a magzat életben maradási esélyeinek növeléséhez.

A transabdominalis amniotomiánál során a beavatkozás célja a magzatvíz mennyiségének helyreállítása, ezáltal a terhesség prolongálása és az oligohydramnionhoz kötődő magzati szövődmények elhárítása. Amniocentesishez használt tűvel a legnagyobb magzatvíz-zsebet megszűrve izotóniás oldat (0,9% NaCl oldat, vagy Ringer-Lactat oldat) juttatható a méh ürébe. Analízisünk alapján a perinatalis túlélést az eljárás szignifikánsan növeli. Ez az eredmény egyrészt a hosszabb latencia idővel, másrészt a pulmonalis hypoplasia előfordulásának csökkenésével magyarázható. A prognózis szempontjából az amniotomiát követő magzatvízvesztés mértéke kulcsfontosságú. Amennyiben az oligohydramnion 48 órán belül visszatér és sorozatos amniotomiák szükségesek, rosszabb neonatalis túlélés és a tüdőhypoplasia gyakoribb előfordulása várható. Ugyanakkor intakt magzatburok mellett jelentkező oligohydramnion esetén a sorozatban végzett amniotomiás kezelés a neonatalis kimenetel javulásával jár.

Az elmúlt időszakban a terhesség alatti invazív diagnosztika mellett az intrauterin sebészeti eljárások is elérhető lehetőséggé váltak a szülészeti gyakorlatban. A beavatkozások egyik leggyakoribb szövődménye az iatrogen burokrepedés, amely 1,7-30% gyakorisággal fordul elő a beavatkozás típusától függően. Az ilyen jellegű burokrepedések kezelésére fejlesztették ki az amniopatch technikát, mely során megfelelő arányban izotóniás sóoldatot, thrombocytaszuszpenziót és alvadási faktorokat tartalmazó cryoprecipitátumot juttatnak az amnionürrébe. A bejuttatott összetevők következtében a burokrepedés helyén fehér színű coagulum képződik, amely a magzatburok sérülését elzárja. Tanulmányunk alapján a legmagasabb túlélési arányt ez a módszer adja, míg a pulmonalis hypoplasia és a végtagdeformitások aránya 1% alatt marad. Fontos, hogy a módszer alapvetően csak iatrogen burokrepedés eseteiben alkalmazható, spontán burokrepedések esetében a szabálytalan amnionrés és a társuló fertőzések miatt a módszer javarészt eredménytelen.

Analízisünk alapján elmondható, hogy a 13-26. terhességi hét között jelentkező oligohydramnion kezelésében a vizsgált aktív módszerek eredményessége felülmúlja a konzervatív megközelítés eredményeit. Spontán burokrepedés, illetve intakt magzatburok mellett jelentkező oligohydramnion esetében transabdominalis amniocentesis, míg iatrogen burokrepedés esetében amniopatch technika alkalmazása indokolt.

Súlyos fokú idiopathiás oligohydramnion kezelése transabdominalis amnioinfúzióval

Anyag és módszer

Munkánk során 2009 és 2012 között a Szegedi Tudományegyetem Szülészeti-Nőgyógyászati Klinika Ultrahang Laboratóriumában transabdominalis amnioinfúzióval kezelt terhességek kimenetelét vizsgáltuk. A transabdominalis amnioinfúzió feltételei a következők voltak: 1) súlyos oligohydramnion (magzatvíz index <5); 2) 16-34. terhességi hét; 3) singularis terhesség; 4) negatív hüvelyváladék prolactin teszt; 5) a beteg teljeskörű felvilágosítást követően elnyert beleegyezése. Kizárási kritériumok voltak: 1) idő előtti burokrepedés; 2) aktív vetélés vagy szülés egyéb tünetei; 3) anyai vagy magzati fertőzés jelei; 4) lepényleválás ultrahang vagy klinikai jelei; 5) diagnosztizált, az élettel összeegyeztethetetlen magzati fejlődési rendellenesség; 6) amennyiben a gravida a beavatkozásba nem egyezett bele, illetve beleegyezését visszavonta. Az amnioinfúziót transabdominalisan, ultrahang ellenőrzés mellett végeztük 0,9% NaCl oldat bejuttatásával. A beavatkozást a normál magzatvízmennyiség eléréséig folytattuk. Ezt követően, a korábban esetlegesen nem diagnosztizált fejlődési rendellenességek felismerése érdekében ismételt részletes ultrahangvizsgálat történt. A magzatvíz mennyiségét a beavatkozást követően másnap, majd hetente ellenőriztük. Amennyiben a magzatvíz index újra 5 alá csökkent, a beavatkozást megismételtük. Statisztikai számításokra Kruskal-Wallis tesztet, Mann-Whitney U tesztet, χ^2 próbát és Fisher exact tesztet használtunk, szignifikánsnak a $p \leq 0,05$ eredményt tekintettük.

Eredmények

A beválogatási kritériumoknak összesen 20 terhes felelt meg. Az első amnioinfúzió időpontjában az átlagos terhességi kor 22,6 hét (16-33,9) volt. Amnioinfúzió egy alkalommal történt 14 terhességben, két alkalommal 3 terhességben, három alkalommal 2 terhességben és négy alkalommal 1 terhességben. A beavatkozások 70%-a a második trimeszterben történt. Tíz esetben (50%) az amnioinfúziót spontán vetélés követte. Ezek közül négy terhességben a beavatkozás kezdetén a retroamniális tér telődését figyeltük meg, a spontán vetélés mind a négy esetben 48 órán belül megindult. A retroamniális telődést a 4. ábra (Figure 4. – 33. oldal) mutatja be. Egy terhességben már a harmadik trimeszterben a magzat méhen belüli elhalása igazolódott. Kilenc graviditás végződött élveszüléssel. A latencia idő átlagosan $27,6 \pm 37,2$ napnak bizonyult. A beavatkozások időrendjét és kimenetelét sematikusan a 3. ábra (Figure 3. – 31. oldal) mutatja be. A sorozatos amnioinfúzióban részesült terhességek esetén a latencia szignifikánsan hosszabb volt az

egyszeri beavatkozásban részesülők eredményénél (69 nap versus 10 nap, $p = 0,002$). A vetéléssel és a szüléssel végződő esetek összehasonlítása látható a 7. és a 9. táblázatban (Table 7. – 32. oldal, Table 9. – 35. oldal) (a méhen belüli elhalással végződő esetet a statisztikai analízisből kizártuk). A szüléssel végződött esetek jellemzői kiemelve a 8. táblázatban (Table 8. – 34. oldal) láthatóak.

Megbeszélés

Vizsgálatunkban a második trimeszteri vetéléseknek köszönhetően a magzati veszteség a várakozást felülmúlta (55%). Ez az eredmény eltér a szakirodalomban közölt adatoktól, ahol a perinatalis halálozás csökkenését írták le amnioinfúzióval kezelt terhességekben. Tapasztalataink szerint amennyiben a beavatkozást követően 3 napon belül spontán burokrepedés következik be, vagy az amnioinfúzió során retroamniális telődés látható, a vetélés kockázata rendkívül magas.

Minél korábban alakul ki a súlyos oligohydramnion, a burokrepedés és a spontán vetélés esélye annál magasabb. Terheseink döntő többségében (75%) a magzatvíz mennyiségének csökkenése a második trimeszter folyamán jelentkezett. Amennyiben 3 napon belül nem történik burokrepedés, a terhesség prolongálásának esélye szignifikánsan emelkedik, de az esetek nagy részében (62,5%) több alkalommal végzett amnioinfúzió válik szükségessé. Új megfigyelésként inverz összefüggést találtunk az amnioinfúzió volumene és a spontán burokrepedés esélye között. A beavatkozások során anyai szövődmeny nem fordult elő. Ugyanakkor vizsgált terheseink között a korai lepényleválás jelentős gyakoriságot (15%) ért el. Más tanulmányok hasonló eredményt közölnek, de úgy tűnik, hogy a korai lepényleválásért nem az amnioinfúzió, hanem maga az oligohydramnion a felelős.

Az irodalmi adatokat is figyelembe véve az antepartum amnioinfúzió lehetséges megoldás az idiopathiás oligohydramnion kezelésében, de ennek ellenére a magzatvíz mennyiségének második trimeszterben jelentkező csökkenése továbbra is rossz prognózist jelent.

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Appendix